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Follow-up of Breast Cancer Patients Stage I–II: A Baseline Strategy

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In 430 stage I–II breast cancer patients the cost-benefit of investigations during follow-up have been studied. Median follow-up time was 8 years and 128 patients had relapsed, 91 with metastatic disease. High costs of routine chest X-ray, limited skeletal X-ray and bone scan examinations were associated with low incidence of diagnosed relapses not suspected otherwise. In the eight blood analyses examined, increases of more than 10 mm/h in erythrocyte sedimentation rate (ESR), 20 U/l in γ-glutamyltransferase (GT) or 60 U/l in alkaline phosphatase (ALP) resulted in a combined sensitivity of 55% and specificity of 91% for relapses with distant metastases. Elevation of at least two blood tests gave a combined sensitivity of 31% and a specificity of 98%. The importance of using individual reference values in screening for recurrences is emphasised. Symptomatic relapse or relapse detected at interval visits were not independent prognostic factors. The blood tests ALP, ESR and GT were strong predictors of survival measured from relapse which increase their legitimacy in follow-up. A more frequent follow-up for patients with 4+ involved nodes is proposed: three visits annually the first 5 years vs. two visits annually for the others. We conclude that history, clinical examination, ALP, ESR and GT are sufficient as a baseline screening for relapse in breast cancer patients.
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INTRODUCTION

DIFFERENT OPINIONS exist regarding the necessity of follow-up, the frequency of follow-up visits and the value of routine examinations in breast cancer patients [1–8]. The trend appears to be towards fewer investigations during follow-up. We advocate follow-up for several reasons: increased risk of cancer in the contralateral breast where early diagnosis can result in downstaging [9], attempt to avoid large tumour masses at relapse which can reduce the possibilities of achieving local control and finally to have a pool of patients for clinical trials. The rising costs in health services, however, stresses the importance of not over investigating this large patient population.

In the present study the following questions were addressed: What is the cost/benefit of standard biochemical evaluation, chest X-ray, limited skeletal X-ray and bone scan in the diagnosis of relapse? Are symptomatic relapse or relapse detected at interval visits independent prognostic factors? Do all patients require the same follow-up frequencies?

PATIENTS AND METHODS

Patients

This study of the follow-up routines was part of a Scandinavian multicentre study of adjuvant chemotherapy and immunotherapy [10]. All patients were examined with a set of biochemical parameters, chest X-ray and bone scan before surgery. The TNM classification (UICC-1974) was used for staging. From 1977 to 1982, 430 consecutive T_0N_0-$T_2N_1M_0$ patients with breast cancer were included in the study. Of these, 288 (67%) patients were node negative, 236 (55%) had tumour size < 2 cm, 150 (35%) were < 50 years and 151/367 (41%) had oestrogen receptor levels < 10 pmol/g protein.

Treatment

Radical (Halsted), modified radical (Patey) or simple mastectomy was performed in 160, 231 and 39 patients, respectively. The mean number of axillary lymph nodes removed was 12. All patients received one perioperative chemotherapy course. The patients were randomised into one of four groups: immunotherapy, prolonged chemotherapy, both of these or no further adjuvant treatment. The chemotherapy given was CMF (600 mg cyclophosphamide, 50 mg methotrexate and 750 mg 5-fluorouracil days 1 and 8, start of new cycle day 28) [10]. Mean number of courses completed were 10 (range 1–12). None of the patients received adjuvant tamoxifen or radiotherapy.

Follow-up scheme and estimation of costs

During the first, second, third to fifth year and later, the patients had 4, 3, 2 and 1 follow-ups annually, respectively. Number of visits and examinations were calculated from the first regular control to relapse or to June 1988. This follow-up time ranged from 6 to 11 years, median 8 years. 5 patients were lost to follow-up, the first after 6 years. At each control visit standard blood analyses were performed. Chest X-ray, limited skeletal X-ray (thoraco-lumbar spine, pelvis and upper femur) and bone scan were done annually in asymptomatic patients, mammography of the contralateral breast every second year. Few violations of this design were noticed the first 7–8 years of follow-up. The costs were estimated by including material consumption and

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salaries only. The 1990 prices were: bone scan US$95, limited skeletal X-ray US$87, chest X-ray US$28 and for the eight blood analyses US$12.

Relapse

The time of relapse was defined as when the clinician concluded with relapse in the medical records and filled out the trial relapse form. Regional relapse was defined as involvement of the ipsilateral axillary or supraclavicular lymph nodes. A new primary cancer of the contralateral breast was not coded as a relapse. The diagnosis of liver metastases was confirmed by ultrasonography. Lung metastases, pleural effusions or mediastinal involvment were verified by chest X-ray. As a part of this follow-up study a radiologist and a nuclear medicine specialist coded the earlier routine descriptions of bone scans and X-rays for patients with skeletal relapse. The following codes for pathological changes were used: 1, normal; 2, uncertain; 3, suspect; 4, metastatic changes. The time when code 4 appeared defined the time of earliest sign of skeletal relapse. In order to evaluate the value of the routine descriptions of bone scans and X-rays delivered to the clinicians, no retrospective review of the films were performed.

Blood analyses

Standard blood analyses were erythrocyte sedimentation rate (ESR), haemoglobin (Hb), leucocyte and thrombocyte counts, alanine aminotransferase (ALAT), alkaline phosphatase (ALP), γ-glutamyltransferase (GT) and lactate dehydrogenase (LD). These were registered (1) preoperatively, (2) 6 months after surgery or 6 months after end of CMF chemotherapy, (3) in relapse free patients the last available set, (4) for relapsing patients the last control before relapse and (5) at relapse. The mean values of the preoperative and the first control samples were used as representative for the period of diagnosis. The blood tests were recorded prospectively but evaluated retrospectively. Thus the thresholds for blood tests derived in this study did not have an impact on the diagnostic approach during the study.

False positive changes in the blood analyses which had increased significantly at relapse, were studied in 10 subsequent visits in 124 and 230 patients without relapse [1240 samples for lactate dehydrogenase (LD) and γ-glutamyltransferase (GT), 2300 samples for erythrocyte sedimentation rate (ESR) and alkaline phosphatase (ALP)]. A combined specificity for ESR, GT and ALP was estimated using 100 patients with complete data (1000 samples). The last blood analyses were taken at a median of 7 years from diagnosis. The samples were consecutively recorded, except follow-ups with a history/diagnosis of infection, these follow-ups were omitted.

Recommended methods for routine enzyme determinations were used [11, 12]. Coulter counter (model S, S Plus or S Plus III) was used for the haemoglobin determinations and the blood cell counts. Platelets were counted with a Technicon Autocounter, Coulter Thrombocounter (S Plus or S Plus III). For ESR a modification of the IFSH standardised method, the Westergren method, was used [13].

Statistical methods

The Wilcoxon's signed rank test was used to calculate the probability values for paired data. For two-way frequency tables Pearson χ^2 test of independence was used. A logistic regression model was used to identify those variables which best characterised the patients with asymptomatic or interval relapse [14]. Analysis of variance with repeated measures (BMDPC-2V) was used to test the hypotheses of no differences in ALP, ESR, GT and LD levels at 10 subsequent follow-ups [14].

The Kaplan–Meier product-limit method was used to estimate the probabilities of surviving. Differences between survival curves were tested by the log rank test. 5 patients died of other diseases without relapse of their breast cancer. Their deaths were treated as censored observations (under risk until death). When analysing symptomatic relapse and interval relapse as prognostic factors, time from diagnosis to last observation was used in order to eliminate detection (of relapse) lead time bias. The Cox proportional hazards model was used to simultaneously analyse the importance of several prognostic factors. The proportional assumption in the Cox model was examined with plots [14]. The cut-offs giving the best prediction of survival and satisfactory plots of proportional hazards were selected. The statistical software of BMDP (BMDP/386) was used [14].

RESULTS

Relapse patterns

128 patients relapsed during a median follow-up of 8 years. The annual relapse rates in relation to nodal status are shown in Table 1. The relapse rate was highest 2 – 5 years from diagnosis, and then declined. The annual relapse rate in this period was 5–7% for all patients with a maximum of 32% for patients with four or more nodes involved. In 32/128 patients (25%) relapses were diagnosed at interval visits. The presence of symptoms, CNS involvement or locoregional recurrence was significantly more frequent in these compared to patients with relapse detected at scheduled visits.

37 patients had locoregional recurrences only, while 91 presented with metastases (Table 2). Of all 128 recurrences, 75 (59%) were symptomatic, 29 (23%) asymptomatic and detected clinically and 24 (18%) were asymtomatic and suspected/detected by blood tests, bone scans or X-ray examinations only. Stage 2 primarily, distant disease and relapse detected at interval visits were significantly more frequent characteristics of the patients with symptomatic versus asymptomatic relapse.

Contralateral breast cancer occurred in 16 patients, 5 of these were less than 50 years of age. 3 were detected by the patient herself, 5 by clinical examination and 8 by the screening mammo-

Table 1. Time from diagnosis to relapse in relation to the number of involved axillary lymph nodes

	Nodes 0 (n=288)		Nodes 1–3 (n=91)		Nodes 4+ (n=51)	
	Relapses					
Years from diagnosis	n=61		n=30		n=37	
	n	%*	n	%*	n	%*
0 – 1	2	1	2	2	8	16
1 – 2	13	5	7	8	9	21
2 – 3	11	4	5	6	3	9
3 – 4	12	5	3	4	10	32
4 – 5	10	4	5	7	4	19
5 – 6	5	2	4	6	1	6
6 – 7	6	3	1	2	1	6
7 – 8	2	1	2	4	0	0
8 – 9	0	0	0	0	1	10
9 –10	0	0	1	4	0	0

* Per cent of patients at risk at the beginning of each interval.

Table 2. Location of relapses in 128 of 430 breast cancer patients

Locoregional recurrences (*n*)	37	
Chest wall		22
Supraclavicular		12
Axillary		3
Distant metastases (*n*)	91	
Contralateral axilla/supraclavicular		5
Lung, pleural effusion, mediastinum		30
Liver		13
CNS		7
Skeletal		56

Of patients with distant metastases 24 had several sites involved and 15 had simultaneous locoregional recurrences.

gram. 2 of the contralateral cases were node positive, none had distant metastases at diagnosis, but 3 of these patients developed distant metastases later.

In 12 patients another primary cancer was diagnosed during follow-up (3 colorectal, 2 bladder, 1 renal pelvis, 4 uterine cervix, 1 endometrium and 1 malignant melanoma). 1 of these patients later developed metastases and died.

Changes of routine blood parameters

None of the 8 blood tests examined changed significantly in patients with locoregional relapse or contralateral new primary. In patients relapsing with metastases, ALP, ESR, GT and LD increased significantly both at the last control before relapse (median 6 months before) and at relapse (Table 3).

In non-relapsing patients analysis of variance showed no significant changes in ESR and GT during 10 subsequent follow-ups while ALP increased from a mean of 154 to 163 U/l ($P < 0.01$) and LD from 339 to 367 U/l ($P < 0.05$). A maximum of 5% visits with false positive increases for each of the blood samples in non-relapsing patients was set as a limit in the retrospective part of this study. This resulted in the threshold values of 10 mm/h for ESR, 20, 60 and 70 U/l for GT, ALP and LD, respectively. Adding the fourth blood test (LD) did not increase the sensitivity of detecting silent relapses notable, but the number of follow-up visits with false positive increments then rose to 15%. A panel incorporating ALP, ESR and GT provided false positive increases in one of these in 9% (specificity 91%) of the follow-up visits in non-relapsing patients. Increases in two of the three gave a specificity of 98%.

Table 3. Per cent increase of blood values at the last control before and at metastatic relapse (n=84–88*).

Blood analysis		Values at diagnosis	Last control before† relapse		At relapse	
			% increase dif‡		% increase dif‡	
			Median	*P*-value	Median	*P*-value
ESR	mm/hr	13	17	< 0.05	59	< 0.001
γ-GT	U/l	25	41	< 0.001	47	< 0.001
Alkaline phosphate	"	153	10	< 0.01	26	< 0.001
Lactate dehydrogenase	"	366	5	< 0.01	10	< 0.01

* 3–7 missing values.

† Median 6 months between the last control and relapse.

‡ Median per cent increase from diagnosis, each patient used as own control.

At relapse, raised values of ALP, ESR or GT were found in 35%, 39% and 30% presenting with metastases, respectively, one or more of these were evaluated in 48 of 88 patients (55%). Requiring at least two elevated blood values the sensitivity decreased to 31% (Table 4). Of the 48 patients, 37 had symptoms, one was detected clinically and 10 were laboratory detected only. At the last control before relapse (median 6 months), 28 of 84 (33%) patients had one or several elevated values. Increases in blood values for different metastatic sites are outlined in Table 4.

X-ray and bone scan examinations

Bone scans showed pathological changes in 50 of 51 (98%) examined patients relapsing in skeleton, while pathological changes in skeletal X-rays were found in 21 of 53 (40%). Retrospectively, 26 patients (51%) had pathological findings (code 4) in their bone scans at examination(s) median 19 months before relapse was reported. In 1 patient pathological X-ray was found at the last follow-up visit prior to reported relapse.

Follow-up resources

By the last follow-up or relapse the patient group had 5749 visits at the out-patient clinic, 2522 chest X-rays, 1392 mammograms, 2043 limited bone X-rays and 1996 bone scan examinations. Excluding mammograms, the bone scans and X-ray examinations performed had a total cost of US$438.000 (all patients, median follow-up 8 years). ALP, ESR and GT only would have cost US$29.000 compared with US£69.000 for all eight blood analyses.

Survival analysis

Symptomatic or interval relapse were not significant prognostic factors when adjusting for other variables. None of the eight blood analyses were significant predictors of time to relapse or time from diagnosis to death. In univariate analyses of time from relapse to death, five of eight blood analyses were strongly correlated to survival (LD, ALAT, GT, ESR and ALP).

DISCUSSION

In this study 59% of the patients were symptomatic at relapse and 23% asymptomatic, but detected clinically. Is it then necessary to add any laboratory tests to history and clinical examination? The importance of history in the diagnosis of relapse has been emphasised by several authors [3–7, 15–17]. However, a high sensitivity of symptoms at relapse accentuate the problem of symptom specificity during follow-up. One study has reported a specificity of 40% [17]. The latter study included stage II patients who had completed adjuvant chemotherapy, and supports our impression that patients quite often present with complaints that do not result in a diagnosed relapse. Therefore we need some supplements to history and clinical examination in order to facilitate the separation of symptoms indicating relapse and those which do not.

Blood parameters were of no use in detecting contralateral breast cancer or locoregional recurrences. No correlations were found between preoperative levels and prognosis, in contrast to the strong association between elevated blood tests at relapse and later adverse survival. These findings emphasise that standard biochemical evaluation have a limited use which seems to be related to more advanced disease. The thresholds for ALP, ESR

Table 4. Relapses at different sites in relation to symtoms, clinically – laboratory detected and elevated blood values.

Location of metastases	*n*	Symptoms %	Asymptomatic clinically detected %	Laboratory detected only %	Elevated blood values‡ 1* %	2† %
Locoregional only	37	40	60	0	0	0
All metastases	91	66	8	26	56	31
Skeletal + other	56	63	13	24	53	30
Skeletal only	29	62	7	31	42	19
Lung + other	37	65	0	35	70	38
Lung only	14	43	0	57	43	7
Liver +/− other	13	85	0	15	100	92

* One elevated blood value using each patient as her own control; more than 10 mm/h for ESR, 20 U/l for GT or 60 U/l for ALP.
† At least two elevated blood values, same thresholds.
‡ $n=88$ (three missing values).

and GT were chosen in order to obtain a high specificity. In 98% of the visits two of these thresholds were not exceeded in non-relapsing patients. The sensitivity of ESR, GT and ALP was not superior to that of the chest X-ray or the bone scan in diagnosis of relapse. Is a sensitivity of 56% (one elevated blood test) or 31% (two elevated blood tests) worthwhile? All three blood tests were correlated to survival; the higher levels at relapse, the shorter survival. This finding increases their importance in a follow-up programme aimed at diagnosing a relapse in time to avoid unnecessary morbidity, in contrast to as early as possible.

It is difficult to define a threshold for blood values as a "relapse warning". The inter-individual variations in some blood samples were substantial, mean ESR during 10 follow-ups ranged between 3 and 42 mm/h for patients with the lowest and highest mean, respectively. We have therefore used individual reference limits to define a relapse warning level. A cut-off at 50 mm/h for the ESR has been proposed likely for metastases in breast cancer [18]. This resulted in only 16% abnormal ESR tests and the ESR was not regarded as relevant in the follow-up in breast cancer. In our study only 8% of the patients relapsing with metastases had an ESR over 50 mm/h. However, when individual reference limits were used, 39% of our patients presenting with metastases had elevated ESR. In a study using a normal elevated grouping, ALP was not found relevant in the diagnosis of skeletal metastases [19]. This might have been a false negative finding as individual reference limits were not utilised.

Which blood tests are the most useful in detecting recurrent breast cancer? ALP [16, 18, 20, 21], carcinoembryonic antigen (CEA) [16, 18, 21–22], ESR [16, 22], GT [18] and LD [20, 21] have all been reported elevated at relapse or in metastatic breast cancer. A recent study assessing the therapeutic response in metastatic breast cancer reported a good correlation with clinical response or progression for ESR, CEA, ferritin, C-reactive protein and orosomucoid [23]. Our study support the use of ALP, ESR and GT as a baseline screening in asymptomatic patients, while CEA, C-reactive protein [23] or others could be added to the blood test panel when felt necessary to explain symptoms or clinical findings.

In patients presenting with bone metastases, bone scans gave the earliest signs of relapse, at a median of 19 months prior to the clinically confirmed relapse. Bone scans detected metastases in 9 asymptomatic patients with normal skeletal X-rays. The total cost of bone scans was about US$190.000, i.e. US$21.000 for the earlier diagnosis in each of these nine silent skeletal relapses. Depsite a better sensitivity than both history, clinical examinations, blood analyses and skeletal X-ray, we conclude as other authors [5, 7, 15, 19, 20] that bone scans are not routinely indicated in asymptomatic patients. In patients with normal ALP and LD, only 0.95% of bone scans were positive, while both reported tests were more frequently abnormal in metastatic disease [20]. These authors concluded that a few blood tests (ALP and LD) can replace bone scan in the screening of skeletal metastases.

Routine chest X-ray in the follow-up is of greater controversy. Different recommendations exist; performing no chest X-ray [24], during the first 2 years (stage I–II) [7], in high risk patients only [25] or in all patients [4, 15]. In our study only 6 out of 37 patients presenting with lung metastases were asymptomatic, not detected clinically and without abnormal blood tests. The cost was US$12.000 for the diagnosis of each of the six silent lung relapses. Our study also demonstrates that lung metastases are often accompanied by metastases in other locations. We therefore conclude not to use chest X-ray regularly in asymptomatic patients.

In breast cancer the strongest predictor of recurrence is the number of involved nodes [7]. The mean annual relapse rate in node 4+ patients was 19% in the first 5 years as compared to 4–5% for node 0–3 patients. The annual relapse rate showed a plateau phase lasting up to the 5th year of follow-up, while our follow-up programme reduced the control frequency already from the second year. In two reports the proposed annual visit frequency was the same the first 4–5 years (two or four controls annually) [4, 5], while others have suggested a reduced frequency from the 2nd or 3rd year [2, 7]. Based on the higher relapse rate for node 4+ patients compared to those with less nodes involved, we suggest more frequent follow-up for these patients. For the first 5 years in patients with three or fewer involved nodes: two visits annually and in patients with greater than four nodes, three visits annually. From the 6th year, one visit annually for all patients.

This will imply a reduction from 14 to 10 visits (29%) during the first 5 years for our node 0–3 patients (the majority of the

Table 5. Proposed follow-up programme for breast cancer stage I–II

Schedule of follow-up:
0–3 nodes : 2 × per year for 5 years, thereafter annually.
4+ nodes : 3 × per year for 5 years, thereafter annually.
History/examination — no indication of relapse:
Blood test: ESR, GT, ALP.*
History/examination — suspected relapse:
Blood test: ESR, GT, ALP + CEA and CRP.†
Optional: X-ray, bone scan.
Mammography contralateral breast: every second year.

* If at least two elevated; new control (using each patient as her own control; more than 10 mm/h for ESR, 20 U/l for GT, 60 U/l for ALP).
† Individual assessment.

patients) and an increase from 14 to 15 controls for node 4+ patients. Interval relapses cannot be avoided. In patients with 0–3 involved nodes 14 relapses were diagnosed at interval visits during the first 5 years. If this new schedule leads to an increase in the interval relapses by, for example 50%, the increase (7 patients) will still constitute a minor group of the original patient population. Locoregional recurrences were more frequent in the patients relapsing at interval visits. Several interval relapses could therefore be of concern, but survival after locoregional relapse was not worse for interval diagnosed patients, contrary to one earlier report [2]. Furthermore, interval or asymptomatic relapse was not a significant prognostic factor when adjusting for other variables. Others have shown that deviations from planned follow-up examinations do not affect the prognosis [3].

For breast cancer patients the risk of developing a contralateral neoplasm is three to five times higher than the risk of developing the first breast cancer [26]. A significant excess of other second neoplasms following breast cancer has been found in patients followed for more than 10 years [27]. This emphasises that one purpose of the follow-up should be early detection of new primary neoplasms [7]. Annual mammography of the contralateral breast is commonly performed [4, 7], and results in the diagnosis of more early stage cancers than clinical examination alone [26]. To our knowledge, no studies have compared different intervals for screening mammography of the contralateral breast in breast cancer patients. Our data do not give an answer to this question. The closest resemblance are results obtained from mass screening [28]. Based on these results we will increase the interval for mammography of the contralateral breast to 2 years.

When using only three blood tests as laboratory screening for recurrent breast cancer, the costs of laboratory examinations per operated patient could be reduced by 94%. However, our original follow-up programme was quite heavy and inevitably would have had to be reduced. Our suggestions for follow-up are less comprehensive than those from a recent survey [29], and closer to a proposed minimalist policy for breast cancer surveillance [30]. Although our programme was not studied by randomisation, the follow-up was uniform with extensive data sampled prospectively. As long as early diagnosis of recurrent breast cancer do not improve the overall survival, we conclude that the present study gives additional support for a simplification of the follow-up programme (Table 5).

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Hormonal Therapy for Metastatic Renal Cell Carcinoma Combined Androgen and Provera Followed by High Dose Tamoxifen

Rose J. Papac and Mary F. Keohane

The purpose of this phase II study was to determine the effectiveness of hormonal therapy with combined high dose androgen and provera or tamoxifen in patients with advanced renal cell carcinoma. 30 patients with metastatic renal cell carcinoma received testosterone propionate 100 mg intramuscularly (i.m.) 5 times weekly plus provera 400 mg (i.m.) twice weekly until disease progression developed. 20 patients, most of whom had previously failed to respond to androgen and provera, received tamoxifen 100 mg/m² daily. Of the 30 patients treated with androgen and provera, 3 (10%) developed partial responses of brief duration. 2 of 20 patients (10%) experienced tumour response with tamoxifen, one instance of complete disappearance of pulmonary metastases in a patient whose primary tumour was questionably persistent at post mortem and another case demonstrating disease stability. Combined hormonal therapy offers very little therapeutic advantage in advanced renal cell carcinoma. Tamoxifen, in high dose, exerts anti-tumour effects in a small cohort of cases.
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INTRODUCTION

FOR MANY malignant diseases major changes in outcome have resulted from extensive trials with antineoplastic agents including newer hormonal agents, cytotoxic drugs, and biological response modifiers, as well as the innovative use of combined therapeutic modalities. Renal cell carcinoma, however, remains a neoplastic disease with minimally effective systemic therapy, most recently interleukin-2 or combinations of biological response modifiers have achieved clinical importance [1, 2].

Hormonal therapy, because of its low toxicity, has been a durable approach to the management of renal cell cancer. Bloom and Wallace reported the initial clinical studies with androgen and progestational agents over 25 years ago [3]. Since then the response rates have fluctuated between 0 and 20%, and are generally 10% or less [4, 5]. In the past two decades several groups have demonstrated the presence of oestrogen and progesterone receptors in renal tumour tissue [6, 7]. There is little correlation between the presence of receptors and response to hormonal therapy. Since the binding affinity of the receptors is considered weak, it is postulated that large doses of hormones might be required to exert significant antineoplastic effects [6].

This prospective study was initiated to determine whether the simultaneous use of two hormones with known antitumour effects in renal cell cancer would exert additive response and whether administration of high dose antioestrogen could yield antineoplastic effects in renal cell cancer.

PATIENTS AND METHODS

Patients

30 patients with a histological diagnosis of renal cell carcinoma were eligible for the study (Table 1). None had received prior chemotherapy, hormonal treatment nor radiotherapy to the primary tumour site. 15 patients had had prior nephrectomy. There were 29 males and 1 female. The median age was 62 with a range of 47 to 88 years. Patients had evidence of measurable progressive disease by palpable masses, X-ray, computer tomography (CT) and/or bone scan. The median time from diagnosis to treatment for all patients was 6 months with a range from 1 to 60 months. Before therapy patients were evaluated by history, physical examination, complete blood counts, SMA 20, chest X-ray, CT scans of the abdomen, chest, brain and bone scans.

Treatment schedule

Therapy with androgen and provera was as follows: testosterone propionate was administered as 100 mg intramuscularly (i.m.) 5 times weekly; provera was given simultaneously, 400 mg

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